REMARKS

The Office Action dated October 20, 2003 has been received and carefully studied.

By the accompanying amendment, the specification has been amended to provide the Abstract on a separate page.

The Examiner maintains the rejection of claims 1-3, 7-13 and 19 under 35 U.S.C. §102(b) as being anticipated by Polivka I (CS 263993) or Polivka II (Coll. Czech. Chem. Commun. 1989, 54(9), 2443-69), wherein pure enantiomers of ketotifen and their biological activities are described. The Examiner states that the administration of a pure enantiomer of ketotifen to an animal in need thereof would inherently lead to the corresponding norketotifen, 10-hydroxy ketotifen and 10-hydroxy-norketotifen, which are metabolites of ketotifen. The Examiner states that the lack of sedative side effects is inherent in the compound.

The rejection is respectfully traversed.

Polivka et al. first reported that ketotifen exists in optically active forms despite its lack of chiral carbons. From reading Polivka I and II, it can be concluded that the isomerism results from restricted rotation and that this restriction may be offered by the 10-keto group and the methyl-group on the piperidine nitrogen. This is indeed a very rare type of isomerism that is referred to as "atropisomerism".

Polivka I and II are silent as to whether the structurally similar compounds but lacking the 10-keto group or the methyl-group on the piperidine nitrogen can form chemically or biologically stable atropisomers. Polivka I and II are silent as to whether the compound norketotifen (a natural metabolite of ketotifen) is a non-chiral chemical entity, and are silent as to whether norketotifen is a mixture of chemically stable atropisomers. Stated differently, in view of the rareness of atropisomerism, one skilled in the art would have no reasonable expectation that norketotifen would form stable

atropisomers simply because ketotifen does. *Indeed, the expectation is that norketotifen would not form stable atropisomers, since an aliphatic group that is believed to be responsible for the restricted rotation in ketotifen (the methyl group on the piperidine nitrogen) is absent in norketotifen.*

In addition, by the accompanying amendment, claim 1 has been amended to recite a pharmaceutical composition comprising the S-isomer of norketotifen free of sedative side effects.

The Examiner maintains the rejection of claims 6-15 and 18-20 under 35 U.S.C. §103(a) as being unpatentable over Polivka I or Polivka II in view of Le Bigot and Bourquin and Kofler. The Examiner admits that Polivka I and II do not specifically disclose the enantiomers of norketotifen, hydroxy ketotifen and hydroxy-norketotifen, but states that administration of a pure enantiomer of ketotifen to an animal would lead to the corresponding compound, since they are known metabolites as shown by Bigot. The Examiner also considers that the lack of side effects of the enantiomer is intrinsic to the compound.

The rejection is respectfully traversed.

Claim 6 recites the method for synthesis of stereochemically active norketotifen. Thus, the corresponding isomer if ketotifen is converted to its nor-intermediate, followed by cleavage catalyzed with Cd/Pb. In contrast, Example 3 of Bourquin teaches the synthesis of 10-hydroxy ketotifen. It is not converted to its nor-intermediate, and Cd/pb is not used. Accordingly, the instant synthetic method is nowhere disclosed or suggested.

With reference to claims 7-15 and 18-20, some background information concerning ketotifen is relevant. Specifically, the 30-year old drug ketotifen is an antihistaminic compound of "Generation 1", which means that the compound inhibits histamine H-1 receptors, but also has sedative side effects. As a matter of fact, ketotifen is significantly more sedating than any other Generation-1 compound, such as diphenhydramine (Benadryl®), and thus ketotifen has never been introduced as an

oral therapy for allergies in the United States. The sedative side effects of ketotifen are so severe that doses of more than 1 or 2 mg cannot be used.

Outside the United States, ketotifen is used for the treatment of patients suffering from diseases such as asthma and atopic dermatitis, however only at very low doses (usually 1 mg or less). The reason for the therapeutic activity of ketotifen in such diseases is not the antihistaminic activity of the drug, but rather the unique anti-inflammatory effects of the compound. Thus, ketotifen is a so-called "mast cell stabilizer", which means that the drug inhibits the release of inflammatory mediators from mast cells and other pro-inflammatory cells. Ketotifen has the reputation of being "mildly" effective and having an onset time of several weeks before it begins having therapeutic effects in patients. The weak activity and delayed onset time are considered to be due to the fact that ketotifen can only be given in extremely low doses because of the dose-limiting sedative side effects of the drug. To achieve optical therapeutic effects, the drug should be used at doses of about 10 mg, which of course would induce sleep in most individuals.

The present inventors have unexpectedly found that practically all of the therapeutic activity after administration of ketotifen to patients with asthma or atopic dermatitis is due to the anti-inflammatory effects of the metabolite norketotifen, rather than to ketotifen itself. This is in itself a remarkable and unexpected finding of a drug that has been intensively studied for more than three decades -- over 1000 publications on various aspects of ketotifen exist!

What is even more surprising is the fact that norketotifen was found by the present inventors to be almost free from sedative side effects. Thus, not only did the present inventors discover that the anti-inflammatory activity of ketotifen resides in norketotifen, but they also discovered that norketotifen does not cause the serious dose-limiting sedative side effects of ketotifen. It is extremely unusual that a metabolite, like norketotifen, that carries the therapeutic activity of the parent

compound, does not also carry the side effects of the parent compound.

In addition, as mentioned above, the present inventors have also found that norketotifen is chiral, consisting of two atropisomers, R-norketotifen and S-norketotifen. The present inventors found that although both atropisomers were equally active as anti-histamines *in vivo*, it was unexpectedly found that S-norketotifen was twice as potent as R-norketotifen as a "mast cell stabilizer", suggesting that the S-isomer is significantly more potent than the R-isomer and the racemate as an anti-inflammatory agent. Very unexpectedly, it also was found that the S-isomer is completely free from sedative side effects, while the R-isomer was found to carry all of the (admittedly weak) sedative side effects of norketotifen.

Accordingly, claims 7 and 20, and claims dependent thereon, are believed to be allowable, since none of the cited references discloses or suggests that the diseases recited could be effectively treated or prevented by administering the S-isomer of norketotifen while eliminating the dose-limiting sedative side effects of ketotifen.

The Examiner rejects new claim 20 under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner requires that the method claim recite the amount of composition administered. By the accompanying amendment, claim 20 has been amended to depend from claim 7. It is believed that the amendment overcomes the rejection.

The Examiner rejects claims 7-15 and 18-20 under 35 U.S.C. §112, first paragraph, as being non-enabling. The Examiner states that the specification does not enable the use of the compounds to treat or prevent the diseases recited.

By the accompanying amendment, claim 7 has been amended to recite a method of treating. Methods of preventing various disorders have been deleted from the claims. In addition, claim 7 has been limited to administering the S-isomer of norketotifen. Applicants respectfully submit that the

skilled artisan would have a reasonable expectation that administration of this compound would be effective for treating the disorders recited.

The Examiner rejects claims 1-3, 6-15 and 18-20 under 35 U.S.C. §102(a) as being anticipated by Aberg I, WO 98/56381 or Aberg II, WO 98/43640.

Although each of these references discloses norketotifen, they do not disclose that norketotifen has atropisomers, nor do they disclose or suggest pharmaceutical compositions comprising the S-isomer of norketotifen that is completely free of sedative side effects.

The Examiner also rejects claims 7, 9, 10, 12, 13-15 and 18-20 under the judicially created doctrine of obviousness-type double patenting of claims 1-7 of U.S. Patent No. 6,207,684.

By the accompanying amendment, the claims have been limited to pharmaceutical compositions comprising the S-isomer of norketotifen, and methods of treating various disorders by administering the S-isomer of norketotifen. The unexpected absence of sedative side effects in the S-isomer is nowhere disclosed or suggested in the '684 patent, and thus it is believed that a terminal disclaimer is no longer necessary.

Reconsideration and allowance are respectfully requested in view of the foregoing.

Respectfully submitted,

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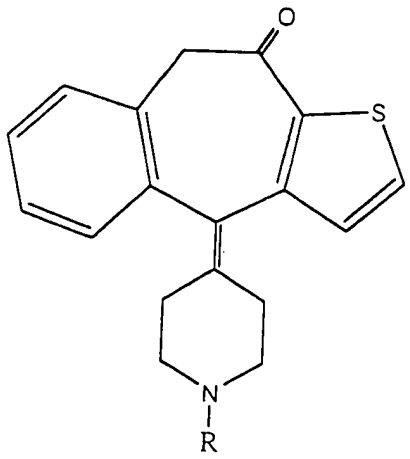
Amendment to the Claims

This listing of claims replaces all prior versions, and listings, of claims in the application.

Listing of Claims:

1. (Currently amended) A pharmaceutical composition comprising the ~~The stereochemically isomeric forms~~ S-isomer of a compound of the structure:



where R is H, and pharmaceutically acceptable salts and solvates thereof, together with a pharmaceutically acceptable carrier, said composition being free of sedative side effects.

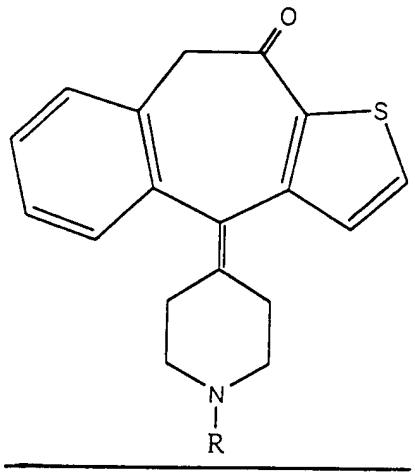
2. (Cancelled)

3. (Cancelled)

4. (cancelled)

5. (cancelled)

6. (Currently Amended) A method for synthesis of the stereochemically active compounds of the structure:



wherein R is H, ~~according to claim 1,~~ being of the R- or S-configuration, comprising the conversion of the corresponding stereochemical isomers of ketotifen into their 1-(2,2,2,-trichloro ethoxycarbonyl) nor-intermediates, followed by Cd/Pb-catalyzed cleavage to the products.

7. (Currently amended) A method for ~~preventing or~~ treating a disease selected from the group consisting of respiratory disorders, allergic disorders, dermal disorders, gastrointestinal disorders and ocular disorders, which comprises administering to a mammal in need thereof a therapeutically effective amount of the S-isomer of norketotifen ~~a compound selected from the group consisting of racemic norketotifen and stereochemical isomers thereof, the S-isomer of ketotifen,~~ or pharmaceutically acceptable salts or solvates thereof, while ~~avoiding~~ eliminating the dose-limiting

sedative side effects of ketotifen.

8. (Original) The method of claim 7, wherein said respiratory disorder is selected from the group consisting of chronic obstructive pulmonary disease (COPD), asthma, cough, bronchitis and bronchial hyperreactivity.

9. (Original) The method of claim 7, wherein said allergic disorder is selected from the group consisting of allergic rhinitis, urticaria, allergic conjunctivitis and allergic keratitis.

10. (Currently amended) The method of claim 7, wherein said dermal disorder is selected from the group consisting of atopic dermatitis, urticaria, other itching or inflammatory conditions and psoriasis.

11. (Original) The method of claim 7, wherein said gastro-intestinal disorder is selected from the group consisting of hypersecretory syndromes including the Zollinger-Ellison syndrome, gastric irritation, enteritis, gastric and duodenal ulcers, gastric reflux, acid indigestion, motility disorders, and heartburn.

12. (Original) The method of claim 7, wherein said ocular disorder is selected from the group consisting of conjunctivitis, keratitis, blepharitis, episcleritis, scleritis, uveitis, neuritis, arteritis and sympathetic ophthalmia.

13. (Original) The method of claim 7, wherein the therapeutically active compound or a pharmaceutically acceptable salt or solvate thereof is administered by inhalation or nasal insufflation or by parenteral, topical, dermal, transdermal, rectal, sublingual, conjunctival or oral administration.

14. (Original) The method according to claim 7, wherein the therapeutically active compound or a pharmaceutically acceptable salt or solvate thereof is administered orally.

15. (Original) The method according to claim 7, wherein the therapeutically active compound or a pharmaceutically acceptable salt or solvate thereof is administered orally in an extended release

formulation.

16. (cancelled)

17. (cancelled)

18. (Original) The method according to claim 7, wherein the amount of the therapeutically active compound is administered from about 0.5 mg to about 200 mg, one to four times per day.

19. (Original) The method according to claim 7, wherein a solid, semi-solid, liquid, suspension, aerosol or topical or transdermal pharmaceutical composition, comprising a therapeutically effective amount of the therapeutically active compound, or a pharmaceutically acceptable salt or solvate thereof, is administered in combination with a pharmaceutically acceptable carrier or carrier system.

20. (Currently amended) ~~A~~ The method according to claim 7, wherein said S-isomer of norketotifen ~~of administering to a mammal in need thereof a composition, said composition comprising a therapeutically active amount of racemic or an optically active isomer of norketotifen, or the S-isomer of ketotifen,~~ or a pharmaceutically acceptable salt or solvate thereof ~~together~~ is administered together with one or more drugs of the class consisting of adrenergic antagonists, analgesics, antihypertensive agents, calcium antagonists, antihistamines, anticholinergic agents, antibacterial agents, antiviral agents, antiinflammatory agents, bronchodilators, decongestants, steroids, leucotriene antagonists, lipoxygenase inhibitors, local anesthetics, vasoconstrictors, vasodilators, cough suppressants, and expectorants.

Amendment to the Specification

Please replace the Abstract with the following new Abstract on a separate sheet:

Pharmaceutical compositions including S-norketotifen as the active ingredient, a method of producing S-norketotifen, and methods of treating disorders by administering effective amounts of S-norketotifen. S-norketotifen was found to have antiallergic and anti-inflammatory effects while being devoid of the severe dose-limiting sedative side effects of ketotifen.